Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

1. Abstract

Acronym/Title	Comparative effectiveness of rivaroxaban and warfarin for stroke prevention in multi-morbid patients with nonvalvular atrial fibrillation (Short title: Rivaroxaban vs. warfarin for SPAF in multi-morbid patients)
Report version and date **Author**	v 1.0, 15 NOV 2019 MetaEvidence, LLC: PPD Bayer AG: PPD, PPD, PPD APCER: PPD, PPD, PPD
IMPACT study number	19859
Keywords	NVAF, Rivaroxaban, Renal dysfunction, Effectiveness, Safety
Rationale and background	This proposed study was conducted to obtain a better understanding on the comparative safety and effectiveness of rivaroxaban vs. Vitamin-K antagonist (VKA) for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) in a routine clinical practice. Specifically, the aim of the study was to evaluate the safety and effectiveness of rivaroxaban in multi-morbid patients, such as those with renal impairment. Subgroup analyses from ROCKET-AF (The Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin-K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) had demonstrated consistent treatment effect for rivaroxaban vs. VKA across a wide range of patient types, including those with prior stroke or transient ischemic attack, reduced renal function, prior myocardial infarction, peripheral artery disease (PAD), heart failure (HF), diabetes, hypertension, abnormal body weight, frailty, low stroke risk (CHA_2DS_2-VASc=1), moderate cytochrome P450 3A4 (CYP3A4) inhibitor use (diltiazem or verapamil), or the elderly.

Research question and objectives	The overall goal of this study was to evaluate the comparative safety and effectiveness of rivaroxaban vs. VKA for stroke prevention in patients with NVAF across the risk profiles and comorbidities that reflected on everyday clinical practice.
Study design	A cohort study using administrative claims data was conducted. The aim of the study was to compare rivaroxaban with VKA for stroke prevention in patients with NVAF across the risk profiles and comorbidities that reflected on everyday clinical practice in the United States of America (USA).
Setting	The source population of this study included all the insured individuals in the IBM Watson MarketScan Commercial Claims and Medicare Supplemental Databases. The study time frame spanned from January 1, 2011 to December 31, 2017 (or until the most recent available data). The date of the first fill of oral anticoagulant (OAC) (rivaroxaban or VKA) was defined as the index date.
Subjects and study size, including dropouts	A total of 78,517 NVAF patients were identified who were OAC-naïve (newly initiated on warfarin or rivaroxaban) and had ≥365 days of continuous medical and prescription insurance coverage (study baseline period) prior to the initiation of oral anticoagulation (index date). Patients who were <18 years of age, had <2 ICD-9 or ICD-10 diagnosis codes for NVAF, or had valvular heart disease, VTE, hip or knee arthroplasty, malignant cancer, pregnancy, transient cause of NVAF, or >1 oral anticoagulant prescribed on index date, were excluded. The patients were further assigned to 7 distinctive cohorts on the basis of existing comorbidities (like renal impairment, diabetes, coronary artery disease (CAD)/PAD, HF, or low stroke risk) or comedications at baseline.
Variables and data sources	Patients' baseline characteristics such as age, sex, comorbidities, and comedications were collected at the index date. The outcomes of interest were combined endpoints of stroke or systemic embolism (SSE), ischemic stroke (IS), hemorrhagic stroke, acute kidney injury, kidney failure, major adverse cardiovascular events (MACEs), major adverse limb events (MALEs), major bleeding, and subtypes of major bleeding. Baseline characteristics and outcome events were assessed using diagnostic procedure as

	well as drug codes. Bleeding-related hospitalizations were identified using the Cunningham's algorithm. IBM Watson MarketScan databases that capture longitudinal, individual-level administrative claims data of the US population were utilized for this study. The data elements that were used in the study included health plan enrollment records, participant demographics, inpatient and outpatient medical claims, and outpatient prescription drug-dispensing records. The data included both Medicare supplemental-covered and employer-paid portions of the healthcare encounter.
Results	In NVAF patients of Cohort 1 (excluding those with Stage 5 chronic kidney disease [CKD]/receiving hemodialysis), rivaroxaban was associated with significant risk reductions of acute kidney injury (AKI) by 19%, progression to Stage 5 CKD or hemodialysis by 18%, SSE and IS each by 33%, and intracranial hemorrhage (ICH) by 42%, in comparison with warfarin. No significant difference in major bleeding was observed between rivaroxaban and warfarin users (hazard ratio [HR] 0.98). In NVAF patients with type 1 or type 2 diabetes mellitus (Cohort 2 had T2DM patients >97%), rivaroxaban was associated with a significant risk reduction of AKI by 17%, progression to Stage 5 CKD or hemodialysis by 18%, MACE by 25%, MALE by 63%, major limb amputation by 80%, and endovascular revascularization by 73% in comparison with warfarin. The risk reductions of IS (17-22%), myocardial infarction (MI) (23%), minor limb amputation (28%), SSE (32%), surgical revascularization (34%), hemorrhagic stroke (34%), and ICH (41%) were better with rivaroxaban in comparison with warfarin; however, they did not reach statistical significance. No significant difference in major bleeding was observed between rivaroxaban and warfarin users (HR 0.95-0.97). In NVAF patients with concomitant CAD and/or PAD (Cohort 3), rivaroxaban was associated with a significant risk reduction of major thrombotic vascular event (MTVEs) by 32% and adverse limb events by 56%. Although the rate of major bleeding with rivaroxaban was higher in comparison to warfarin (HR 1.13), it was of no statistical significance (95% CI: 0.84 - 1.52). In NVAF patients with renal impairment (CKD stages 4 or 5 or undergoing hemodialysis) (Cohort 4), rivaroxaban use was associated with a significant 32% lower risk of major

	bleeding compared with warfarin. Rivaroxaban was also associated with a 45% reduction in the risk of SSE vs. warfarin, albeit the 95% confidence intervals (CIs) crossed the line of unity. In NVAF patients with heart failure (Cohort 5), the risk reductions of SSE (18%) and IS (23%) were better with rivaroxaban in comparison with warfarin; however, they did not reach statistical significance. No significant difference in major bleeding was observed between rivaroxaban and warfarin users (HR 0.98). These findings were consistent with those from a sub-analysis from the ROCKET-AF trial. In NVAF patients experiencing polypharmacy (≥5 chronic medications) (Cohort 6), rivaroxaban was associated with a significant risk reduction of SSE by 34% and IS by 40% in comparison with warfarin. In NVAF patients experiencing substantial polypharmacy (≥10 chronic medications), the risk reductions of SSE (56%) and IS (38%) were better with rivaroxaban in comparison with warfarin; however, they did not reach statistical significance. No significant difference in major bleeding was observed between rivaroxaban and warfarin users (HR 1.07-1.08). In NVAF patients with low stroke risk (CHA_2DS_2-VASc score = 1) (Cohort 7), rivaroxaban was associated with a significant risk reduction of SSE (by 59% and 54% at 1-year and 2-year follow-up, respectively) in comparison with warfarin. The risk reduction of IS (51% and 37% at 1-year and 2-year follow-up) and major bleeding (26% and 35% at 1-year and 2-year follow-up) were better with rivaroxaban in comparison with warfarin; however, they did not reach statistical significance.
Discussion	When used in a routine practice in NVAF patients, rivaroxaban vs. warfarin appears to be associated with lower risks of AKI or renal impairment (in those with or without diabetes mellitus), MACE and MALE (in those with diabetes), MTVEs (in those with CAD and/or PAD), and SSE and IS (in those with heart failure or a lower risk of stroke). Moreover, in the setting of polypharmacy, rivaroxaban in NVAF patients is an effective and safe alternative to warfarin. The risk of major bleeding with rivaroxaban is generally comparable to warfarin. Rivaroxaban use in patients with NVAF and Stage 4 or 5 CKD and among those receiving hemodialysis, appears to be associated with less major bleeding compared with warfarin, although additional studies are needed to confirm

	the effectiveness and safety of rivaroxaban in patients with severe kidney dysfunction and to help determine optimal dosing in this population. The fact that the real-world findings in this study are generally consistent with those from Phase III randomized trials of rivaroxaban vs. warfarin in NVAF should provide additional reassurance to clinicians regarding the use of rivaroxaban in people with comorbidities that reflected on everyday clinical practice. As the study used the US claims data, the results therefore are generalizable to an insured US population with NVAF.
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